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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR		ATTORNEY DOCKET NO.
09/385,114	08/27/99	WHITEHOUSE	M	1543.004/121

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JOSEPH H GUTH ESQ
CHIRON CORPORATION
4560 HORTON STREET P O BOX 8097
INTELLECTUAL PEOPERTY R-440
EMERYVILLE CA 94662-8097

EXAMINER	
ROBINSON,H	
ART UNIT	**PAPER NUMBER**
1653	10

DATE MAILED: 12/04/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/385,114	Applicant(s) Whitehouse
	Examiner Hope Robinson	Group Art Unit 1653

☒ Responsive to communication(s) filed on *Sep 18, 2000*.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-37* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-37* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *7*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

1. Applicant's response to the Office Action mailed May 12, 2000 in Paper No. 9 on September 18, 2000 is acknowledged.

2. Claims 10, 19, 20, 21 and 35 have been amended. Claims 35-37 have been added. Claims 1-37 are pending.

3. The objections to the Specification and Abstract have been withdrawn. The rejections under 35 U.S.C. 112, second paragraph have been withdrawn.

4. The following grounds of rejection remain or are applicable:

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 1-9 remain rejected under 35 U.S.C. 102(b) as being anticipated by Baird et al. (U.S. Patent No. 5,155,214, October 13, 1992) based on an angiogenically active fragment.

Baird disclose substantially pure mammalian basic fibroblast growth factors. Further the amino acid residue sequences of bovine and human bFGF are disclosed as well as a DNA chain encoding the polypeptide of the bovine species (see abstract). Baird also disclose that basic FGF has a similar activity in vivo on capillary endothelial cells, therefore, basic FGF is considered an angiogenic factor (see column 1). Baird further discloses a pharmaceutical compositions including bFGF, a bFGF analog, biologically active fragments of bFGF or of analog bFGF, or nontoxic salts thereof dispersed in a pharmaceutically acceptable liquid or solid carrier. In addition, Baird discloses that these pharmaceutical compositions can be used in clinical medicine, both human and veterinary, in acute or chronic administration of diagnostic or therapeutic purposes (see column 3). Baird also disclose the sequence contained in SEQ ID No. 2 with a 100% identity to the sequence in the instant application (see alignment). Therefore, the sequence limitations of the claims are met by this reference.

6. Applicant's arguments on page 20 concerning the rejection under 35 U.S.C. 102(b) is not convincing. In the response applicant asserts that while Baird discloses a bFGF that has the amino acid sequence of SEQ ID NO: 2, Baird fails to disclose the "unit dose composition" of claim 1 with all of its recited elements in the recited amounts for inducing angiogenesis in a human. However, the claim recites a unit does composition comprising about .008 mg to about

7.2 mg of FGF-2 **or** angiogenically active fragment **or** muetin thereof. Baird discloses an angiogenically active fragment and the sequence is identical which is sufficient to anticipate the claimed invention based on the claim language.

7. Claims 1-15 are rejected under 35 U.S.C. 102(b) as being anticipated by Sellke et al. (The Society of Thoracic Surgeons, vol. 65, pages 1540-1544, 1998).

Sellke disclose a method for treating human patients for coronary artery disease (see page 1541, col. 1) comprising administering recombinant human b-FGF also known as FGF-2, to one or more coronary vessels (see Figure 1). The dose of bFGF was 10μg or 100μg per patient, since the average human weight is generally accepted to be 70kg, 0.7μg/kg to 7μg/kg. In addition, Sellke disclose the usage of unit dosages of 1μg or 10μg basic fibroblast growth factor which was implanted in epicardial fat, this dosage fits in the range of about .008mg to about 7.2mg once converted. Therefore, Sellke anticipates claims 1 and 10. In addition, since FGF-2 is also bFGF and has the sequence set forth in SEQ ID No: 2, claims 2-9 and 11-15 are also anticipated. Furthermore, the patients were heparinized prior to cardiopulmonary bypass surgery and the administration of bFGF (see pages 1540-1543). Thus, the limitations of the claims are met by this reference.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 1-37 are rejected under 35 U.S.C. 103 (a) as being unpatentable over Franco (U.S. Patent No. 4,378,347, March 29, 1983) in view of Uchida et al. (American Heart Journal, vol. 130, no. 6, pages 1182-1188, December 1995) and Sellke et al. (The Society of Thoracic Surgeons, vol. 65, pages 1540-1544, 1998).

Franco disclose a method and use of an effective dose of FGF for treatment of myocardial infarct and heart surgery procedures such as coronary bypass operations. Franco disclose that the preferred dosage is about 10μg to 1 gram of FGF per 100 grams of heart which is directly injected into the heart. Franco do not explicitly teach the sequence contained in SEQ ID No. 2.

Uchida teach that angiogenesis and myocardial salvage occur illustrated by, injection through the right atrium into the pericardial cavity of 30 mg basic fibroblast growth factor and 3 mg heparin sulfate. Uchida assert that FGFs act as regulatory proteins that induce the proliferation of a variety of cells and function as an angiogenic factor in vitro and in vivo. Uchida also teach a significant increase in the number of collateral vessels and subsequent salvage of the infarcted myocardium induced by intracoronary injection of bFGF. Furthermore, Uchida teach a

method to administer bFGF selectively and safely into the infarcted area, irrespective of the coronary anatomy and contraindications for coronary interventions. Thus, the method can be widely applied as a therapeutic regimen for myocardial salvage to patients with acute myocardial infarction or as a preventive regimen for myocardial infarction.

Sellke teach a method for treating human patients for coronary artery disease (see page 1541, col. 1) comprising administering recombinant human b-FGF also known as FGF-2, to one or more coronary vessels (see Figure 1). Sellke also teach the use of therapeutic angiogenesis using naked DNA plasmids encoding angiogenic growth factors, DNA delivered by an adenoviral or liposomal vector, or the administration of authentic growth factor proteins to improve perfusion in ischemic regions of myocardium and in patients with peripheral vascular disease. Furthermore, Sellke teach that the delivery of the protein as opposed to the DNA encoding the protein has a potential advantage of simplicity, consistent delivery and safety. In addition, Sellke teach that basic fibroblast growth factor (bFGF) has both angiogenic and mitogenic potential. In addition, Sellke teaches that the angiogenic effect of bFGF is dose dependent and demonstrates the safety and technical feasibility of therapeutic angiogenesis with basic fibroblast growth factor.

Additionally, Sellke teach a dose of bFGF that falls within the range recited in claims 1 and 10. Furthermore, Sellke teach the sequence contained in SEQ ID No: 2 and disclose that the patients were heparinized prior to cardiopulmonary bypass surgery and the administration of bFGF (see pages 1540-1543).

Therefore, it would have been obvious to one of ordinary skill in the art to arrive at the claimed invention as a whole by combining the teachings of the above references because Franco, Uchida and Sellke teach a composition for inducing angiogenesis, the sequence contained in SEQ ID No: 2 with a high sequence identity and a unit dose that falls within the claimed dosage range. In addition, Sellke disclose the benefits of using bFGF.

Furthermore, Uchida disclose that in patients bFGF injected into the coronary artery may not reach the infarcted area, because it may be conjugated with the extracelluar matrix at the site of coronary lesion or may enhance stenosis. Therefore, by administration of bFGF selectively and safely into the infarcted area, irrespective of the coronary anatomy and contraindications for coronary interventions, this method can be widely applied as a therapeutic regimen (see page 1182). One of ordinary skill in the art would be motivated to produce a unit dose composition to be delivered in these areas for treatment of coronary artery disease and myocardial infarction as taught by Franco and Sellke because of the benefits described by Sellke and Uchida. Thus, the claimed invention was within the ordinary skill in the art to make and use at the time it was made and was as a whole, *prima facie* obvious.

9. Applicant on page 20+ reviewed the cited references singularly and concluded that the teachings were divergent and deficient. However, the combined teachings of the above references renders the claimed invention as obvious because an angiogenically active fragment is taught and

the sequence in association with a medicament as claimed. Note also that two new references have been cited to further clarify the rejections on the record.

Conclusion

10. No claim is allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Hope Robinson whose telephone number is (703) 308-6231. The examiner can normally be reached on Monday-Friday from 9:00 am to 6:00 pm (EST).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher S.F. Low, can be reached at (703) 308-2923.

Any inquiries of a general nature relating to this application should be directed to the Group Receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted by facsimile transmission. The official fax phone number for Technology Center 1600 is (703) 308-4242. Please affix the examiner's name on a cover sheet attached to your communication should you choose to fax your response. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG (November 15, 1989).

Hope Robinson, MS

Patent Examiner

KAREN COCHRANE CARLSON, PH.D
PRIMARY EXAMINER